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Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: a randomized trial (CE-MARC 2)

John P. Greenwood PhD¹, David P. Ripley MBChB¹, Colin Berry PhD², Gerry P. McCann PhD³, Sven Plein PhD¹, Chiara Bucciarelli-Ducci PhD⁴, Erica Dall'Armellina PhD⁵, Abhiram Prasad MD⁶, Petra Bijsterveld MA¹, James R. Foley MBChB¹, Kenneth Mangion PhD², Mark Sculpher PhD⁷, Simon Walker MSc⁷, Colin C. Everett MSc⁸, David A. Cairns PhD⁸, Linda D. Sharples PhD⁸, Julia M. Brown MSc⁸, on behalf of the CE-MARC 2 Investigators*

The authors' affiliations:

1. Multidisciplinary Cardiovascular Research Centre & the Division of Biomedical Imaging, Leeds Institute of Cardiovascular & Metabolic Medicine, University of Leeds, UK
2. Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK
3. Department of Cardiovascular Sciences, University of Leicester and NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Groby Road, Leicester, UK
4. Cardiovascular Magnetic Resonance Unit, NIHR Bristol Cardiovascular Biomedical Research Unit, Bristol Heart Institute, University of Bristol, Bristol, UK
5. Acute Vascular Imaging Centre, Radcliffe Department of Medicine, John Radcliffe Hospital, University of Oxford, Headley Way, Oxford, UK
6. Cardiovascular Sciences Research Centre, St. George's, University of London, UK
7. Centre for Health Economics, University of York, York, UK
8. Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, UK

* A complete list of investigators in the CE-MARC 2 trial is provided in the Supplementary Appendix (Table S1).

Corresponding author: Professor John P. Greenwood, Leeds Institute of Cardiovascular & Metabolic Medicine, LIGHT Building, Clarendon Way, University of Leeds, Leeds, LS2 9JT, United Kingdom.

Tel: +44 113 3922650; Fax: +44 113 3922311; E-mail: j.greenwood@leeds.ac.uk

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ABSTRACT

Importance: In patients investigated for suspected coronary heart disease (CHD), rates of invasive angiography are considered too high, with limited data from randomized trials evaluating strategies to reduce this.

Objective: To test the hypothesis that in patients with suspected CHD, cardiovascular magnetic resonance (CMR)-guided care is superior to National Institute for Health and Care Excellence (NICE) guidelines-directed care and myocardial perfusion scintigraphy (MPS)-guided care, in reducing the occurrence of protocol-defined unnecessary angiography.

Design, Setting and Participants: Multi-center, 3-parallel group, randomized trial using a pragmatic comparative effectiveness design. 1,202 symptomatic patients with suspected CHD and a pre-test likelihood 10-90%, were recruited from 6 UK hospitals. First randomization 23rd November 2012; last 12-month visit 12th March 2016.

Intervention: Patients were randomly assigned (240:481:481) to management according to UK NICE Guidelines, or results of CMR, or MPS testing.

Main Outcomes and Measures: The primary endpoint was protocol-defined unnecessary coronary angiography (Fractional Flow Reserve (FFR) >0.8 in all vessels ≥ 2.5 mm diameter or by Quantitative Coronary Angiography (QCA) if FFR not feasible) within 12 months. Secondary endpoints included positive angiography, major adverse cardiovascular events (MACE), and procedural complications.

Results: Patients mean(SD) age was 56.3(9.0) years, 564(46.9%) were women, mean pre-test likelihood was 49.5%(23.8%). After 12 months 102, 85 and 78 patients underwent invasive coronary angiography in the NICE, CMR and MPS-guided care groups; study-defined unnecessary angiography occurred in 69(28.8%), 36(7.5%) and 34(7.1%) patients respectively. Adjusted odds ratio of unnecessary angiography for CMR vs. NICE guided-care was 0.21 (95%CI: 0.12 to 0.34; $p<0.001$) and for CMR vs. MPS 1.27 (0.79 to 2.03; $p=0.32$). Positive angiography proportions were 12.1% (8.2% to 16.9%), 9.8% (95%CI: 7.3% to 12.8%), 8.7% (6.4% to 11.6%), respectively. MACE

were reported in 1.7, 2.5% and 2.5% of patients respectively at minimum 12 months, adjusted hazard ratios: CMR vs. NICE 1.37 (95%CI 0.52 to 3.57); CMR vs. MPS: 0.95 (0.46 to 1.95).

Conclusions and Relevance: In patients with suspected angina, investigation by CMR produced a lower probability of unnecessary angiography than NICE guideline-directed care, with no statistically significant difference between CMR and MPS strategies. There were no statistically significant differences in MACE rates at 12 months post-randomization.

Trial Registration: [clinicaltrials.gov: NCT01664858](https://clinicaltrials.gov/ct2/show/study/NCT01664858)

Key words: Magnetic resonance imaging; single photon emission computed tomography; coronary heart disease; myocardial perfusion scintigraphy; coronary angiography; CT coronary angiography; comparative effectiveness research.

Word Count: 3025

KEY POINTS:

Question: In patients investigated for suspected coronary heart disease, does a strategy involving Cardiovascular Magnetic Resonance (CMR) result in less unnecessary angiography than a Myocardial Perfusion Scintigraphy (MPS) strategy or a national guideline that included direct-to-angiography for high-risk patients?

Findings: In this clinical trial, both CMR and MPS significantly reduced unnecessary angiography rates compared to national guidelines (7.5%, 7.1%, 28.8%, respectively); no statistically significant differences were seen between CMR and MPS. There was no statistically significant difference in MACE rates at 12-months between the 3 groups.

Meaning: Non-invasive functional imaging strategies reduced unnecessary angiography compared to guidelines-directed care.

BACKGROUND

Coronary heart disease (CHD) is a leading cause of death and disability worldwide. Several investigations are available to diagnose CHD, risk-stratify patients and determine the need for revascularization. Myocardial perfusion scintigraphy (MPS) by single-photon emission computed tomography is the most commonly used test worldwide for the assessment of myocardial ischemia, with robust evidence supporting its prognostic value. However, cardiovascular magnetic resonance (CMR) is increasingly recognized as having excellent diagnostic accuracy and prognostic value.^{1,2}

Despite the widespread availability and recommendations for non-invasive imaging in international guidelines,³⁻⁵ invasive coronary angiography is commonly used early in diagnostic pathways in patients with suspected CHD. Evidence from large populations presenting with chest pain has confirmed that the majority will not have significant obstructive coronary disease;^{6,7} a large US study reported that ~60% of elective cardiac catheterizations found no obstructive CHD.⁸ Thus, avoiding unnecessary angiography should reduce patient risk and provide significant financial savings.

Current guidelines for investigation of stable chest pain advocate management based on the pre-test likelihood of CHD.³⁻⁵ However, pre-test likelihood models can overestimate CHD risk, therefore paradoxically increasing the probability of invasive coronary angiography.⁹ To date, there are no large scale comparative effectiveness trials of different functional imaging strategies recommended by current guidelines.

The Clinical Evaluation of MAGnetic Resonance imaging in Coronary heart disease 2 trial (CE-MARC 2) was designed to test the hypothesis that in patients with suspected CHD, CMR-guided care is superior to guidelines-directed care⁴ and MPS-guided care,¹⁰ in reducing the occurrence of unnecessary invasive angiography occurring within 12 months.

METHODS

TRIAL DESIGN

CE-MARC 2 was a multi-center, 3-parallel group, randomized trial. It used a pragmatic comparative effectiveness design,¹¹ to determine efficacy and safety of three strategies (CMR-guided care, MPS-guided care (following ACCF/AHA appropriate-use criteria)¹⁰, and UK National Institute for Health and Care Excellence (NICE) guidelines (CG95)⁴) for investigating patients with suspected CHD. The study was conducted in accordance with the protocol (available with the full text of this article) which was approved by the UK National Research Ethics Service (12/YH/0404) and institutional review boards of the participating centers. Study conduct was in accordance with the Declaration of Helsinki; all patients provided written informed consent. The study protocol and statistical analysis plan are available as an online supplement to the article.

TRIAL POPULATION

Patients with suspected angina pectoris were eligible if they were aged ≥ 30 years, had a CHD pre-test likelihood of 10-90%,^{4,12} and suitable for revascularization. Exclusion criteria included non-anginal chest pain, normal MPS/cardiac computed tomography (CCT) within previous 2-years, clinically unstable, previous myocardial infarction, previous coronary revascularization and contraindication to any study non-invasive imaging test (Supplementary Appendix Table S4).¹¹ Self-reported ethnicity was collected as a known cardiac risk factor.

RANDOMIZATION

Patients were assigned using minimization, incorporating a random element and 1:2:2 allocation ratio¹³ through an automated 24h secure-access telephone service by the Clinical Trials Unit. Allocation was to 1 of 5 equally-sized groups (A:B:C:D:E, stratifying on center, age (30-64, ≥ 65 yrs), pre-test likelihood (10-29%,30-60%,61-90%) and sex) following which management was by NICE guidelines-directed care (A) CMR (groups B or C) or MPS (D or E). Patients randomized to NICE-

directed care were scheduled for CCT, MPS or direct to coronary angiography for those with pre-test likelihoods of 10-29%, 30-60%, and 61-90% respectively.

DIAGNOSTIC TESTING

All investigations were performed and interpreted by certified local physicians using protocols conforming to international standards.¹⁴⁻¹⁷ Quality Assurance was undertaken centrally throughout the trial by blinded, independent, modality-specific imaging experts (Supplementary Appendix Table S3): 10% of scans for each modality at each recruiting center were centrally reviewed for image quality and report accuracy. Detailed protocols for each imaging modality and criteria for reporting a positive result have been published;¹¹ a positive CMR, MPS or CCT resulted in protocol-defined invasive coronary angiography and fractional flow reserve (FFR) measurement.¹¹ FFR (PressureWire™, St Jude Medical, Minneapolis, USA) was performed in all vessels ≥ 2.5 mm with a 40-90% stenosis.¹¹ Where FFR was not possible for clinical/safety reasons, quantitative coronary angiography (QCA) was performed. All FFR and QCA results were analyzed at the Glasgow Angiographic Core-Lab by a single, independent, blinded observer. Positive angiography defined as any lesion with $\text{FFR} \leq 0.8$, or if FFR not performed, a percentage diameter stenosis of $\geq 70\%$ in one view or $\geq 50\%$ in two orthogonal views.

ENDPOINTS

The primary endpoint was protocol-defined unnecessary coronary angiography occurring within 12 months, defined by a normal FFR (or QCA) in all vessels ≥ 2.5 mm diameter. By design this included any unnecessary angiography occurring after a false positive test result, direct to angiography for high-pre-test likelihood patients (NICE group only), and imaging results which were either inconclusive or negative but over-ruled by the responsible physician.¹¹ Secondary endpoints included a composite of major cardiovascular events (MACE: cardiovascular death, myocardial infarction, unplanned coronary revascularization and hospital admission for cardiovascular cause), and positive angiography rates (recommended by the independent Data

Monitoring and Ethics Committee (DMEC)). Complications directly related to trial investigations resulting in prolonged hospital stay/specific treatment were pre-specified as safety secondary endpoints. Quality of life outcomes and cost effectiveness analyses will be reported subsequently.

TRIAL OVERSIGHT

Independent DMEC and Trial Steering Committee (TSC) assessed study conduct, integrity and safety 6-monthly (Supplementary Appendix Table S2).

STATISTICAL ANALYSIS

1200 patients, allowing for 20% non-completion, would provide the study with 99% power to detect a difference in unnecessary angiography between CMR and guidelines-directed care (using 2:1 allocation), and 94% power between CMR and MPS-guided care based on projected unnecessary angiography proportions of 4.5%, 11.7% and 30% in the CMR, MPS and NICE-groups respectively (2-sided 5% significance for continuity-corrected chi-squared test).¹⁸

Logistic regressions were used to model odds of an unnecessary angiogram for CMR- versus both NICE- and MPS-guided management, including stratification factors (treating centers as fixed effects). Analyses used intention-to-treat (ITT) populations and were repeated in per-protocol populations. Multiple imputation (by fully conditional specification) was used for missing baseline, test and endpoint data to ensure all participants could be included in the analysis, and avoid treating unknown values as certainly known (e.g. with mean imputation, no-event imputation).¹⁹

Ten fully-imputed analysis datasets were generated - since the proportion of patients with any missing data was less than 10% - and primary endpoint analyses on each dataset were combined to produce the overall ITT effect using Rubin's rules. The proportion of patients in each group with a MACE at twelve months and absolute differences in MACE rates were calculated. Confidence intervals for proportions and their differences were calculated by exact methods. Time to first MACE was modelled using Cox proportional hazards regression, including stratification and other pre-specified (Hypertension, Ethnicity, Smoking and Diabetes) factors and illustrated using Kaplan-

Meier estimates. CMR and MPS groups were combined into a single 'functional imaging' group to compare unnecessary angiography versus guidelines-directed care in the 61-90% and 10-29% pre-test likelihood subgroups. Subgroup analyses were undertaken by including interaction effects in regression models. Statistical tests were 2-sided and called significant at the 5% level. Analyses used SAS v9.4 (SAS Institute Inc.) after all randomized patients had completed 12 months follow-up; there were no interim analyses.

RESULTS

TRIAL POPULATION

Between November 2012 and March 2015, 13,957 patients were screened of whom 2,205 were eligible (Figure 1 lists reasons for non-eligibility and non-consent). 1,202 (55% of eligible) patients were recruited from six UK centers (Leeds, Glasgow, Leicester, Bristol, Oxford, London (St Georges)) and allocated to guidelines-directed care (n=240) or management by CMR (n=481) or MPS (n=481) (Figure 1).

BASELINE CHARACTERISTICS

Mean(SD) age of patients was 56.3(9.0) years, 638(53%) were male, mean BMI 29.1(5.2) and 1,107(92%) were classified ethnically as white (Table 1). The study population had a substantial burden of cardiovascular risk factors: 150(12.5%) of the patients had diabetes, 458(38.1%) had hypertension, 702(58.4%) were past or current tobacco users, 483(40.2%) had dyslipidemia, and 651(54.2%) had a family history of premature CHD. Patients had a median of 2 of these 5 risk factors. All patients were symptomatic, with 401(33.4%) reporting typical chest pain and 801(66.6%) atypical chest pain as their primary symptom. The assessment of cardiac risk, calculated according to the 2013 atherosclerotic cardiovascular disease risk score from the ACCF/AHA guidelines, showed that 441 of 923 (47.8%) patients had a 10-year risk of events of

7.5% or higher.²⁰ The mean(SD) pre-test likelihood of obstructive CHD according to the Duke Score was 49.5(23.8%).¹²

TEST CONDUCT

Of 481 patients assigned to the CMR strategy, 435(90.4%) had CMR as the initial test (median(Interquartile Range) time from randomization 20(13-34) days), 5(1.0%) had MPS, 5(1.0%) went directly to angiography and 23(4.8%) had no test. Of 481 patients assigned to the MPS strategy, 446(92.7%) had MPS as the initial test (time from randomization 28(22-39) days), 4(0.8%) had CMR, 5(1.0%) went directly to angiography and 21(4.4%) had no test. Of 240 patients assigned to NICE guidelines strategy 56(23.3%) had CCT (time from randomization 34(14-44) days), 86(35.8%) had MPS, 85(35.4%) went directly to angiography and 11(4.6%) had no test. The numbers of patients adherent to receiving both their initial randomized test and per-protocol compliance with their test result were 414(86.1%), 368(76.5%) and 200(83.3%), respectively.

Study sites reported their interpretation of the initial test as positive for CHD in 54/435(12.4%) patients in the CMR group, in 81/446(18.2%) patients in the MPS group and in 19/142(13.4%) patients in the NICE group. There was no difference in revascularization rates (Figure 1) between the 3 groups (P=0.47). The rate of patients with incomplete data required for analysis of the primary endpoint was low: 18/240(7.5%), 50/481(10.4%) and 33/481(6.9%) for NICE, CMR and MPS groups, respectively. Of these, 11/240(4.6%), 23/481(4.8%) and 21/481(4.4%) were related to missing test results for NICE, CMR and MPS groups, respectively.

PRIMARY ENDPOINT

Overall, 265(22.0%) patients underwent at least one coronary angiogram (10 patients underwent 2 angiograms) within 12 months of randomization: 102/240(42.5%) in the NICE group, 85/481(17.7%) in the CMR group and 78/481(16.2%) in the MPS group. The primary endpoint of unnecessary angiography occurred in 69(28.8%), 36(7.5%) and 34(7.1%) and patients respectively. 98(70.5%) of these angiograms had no visual stenosis and were not assessed further, 40(28.8%)

reached the conclusion by FFR and 1(0.7%) involved QCA only. The adjusted odds ratio (95%CI) of unnecessary angiography for CMR versus NICE was 0.21 (0.12 to 0.34; $P<0.001$) and CMR versus MPS 1.27 (0.79 to 2.03; $P=0.32$). Table 2 shows individual components of the primary endpoint. For both comparisons, the primary analysis was repeated in the per-protocol population, with no effect on the trial results. Sensitivity analyses using random center effects or adjusting for further risk factors (hypertension, ethnicity, smoking status) or using the per-protocol population did not change overall trial conclusions (Supplementary Appendix Table S5). Exploratory subgroup analyses showed consistent results across subgroups (Figure 2).

SECONDARY ENDPOINTS

Positive angiography was observed in 29(12.1%)(95%CI 8.2% to 16.9%), 47(9.8%)(95%CI 7.3% to 12.8%) and 42(8.7%)(95%CI 6.4% to 11.6%) patients for NICE, CMR and MPS groups respectively ($P=0.36$). During minimum 1-year follow-up (median 15.8 months, Interquartile range 12.1 to 24.2), 36(3.0%) patients had at least one MACE: NICE 6(2.5%), CMR 15(3.1%), MPS 15(3.1%) (Table 2). Annualized MACE rates were 1.6%, 2.0% and 2.0%, respectively. Adjusted hazard ratios for MACE were: CMR vs. NICE 1.37 (95%CI: 0.52 to 3.57; $P=0.52$); CMR vs. MPS 0.95 (0.46 to 1.95; $P=0.88$). Hard events (cardiovascular death and MI) occurred in 3(1.3%), 5(1.0%), 4(0.8%) in NICE, CMR and MPS groups respectively ($P=0.93$). Figure 3 shows the Kaplan-Meier cumulative incidence estimate of first MACE. Five test complications were reported: CMR (1: mild urticarial reaction), MPS (0), cardiac CT (1: vasovagal episode) and angiography (3: ventricular tachycardia; pseudo-aneurysm & popliteal DVT; right coronary artery spasm & transient ST elevation).

FUNCTIONAL IMAGING ASSESSMENT

Using functional imaging first-line (CMR or MPS) in patients with 61-90% (high) pre-test likelihood of CHD, resulted in substantially reduced odds of unnecessary angiography compared to the NICE group; odds ratio (OR) 0.048 (0.023 to 0.10; $P<0.001$). Among those with <30% (low) pre-test

likelihood, the odds of unnecessary angiography were also numerically lower by a functional imaging approach compared to anatomical (CCT) assessment (OR 0.44; 0.17 to 1.17; P=0.099).

DISCUSSION

CE-MARC 2 was a multi-center, randomized trial in a large community-based population of symptomatic patients undergoing assessment for suspected CHD, in whom further investigation was appropriate according to international guidelines. A CMR-guided strategy significantly reduced unnecessary angiography occurrence, as compared with NICE guidelines-guided care, but was not significantly different from an MPS-guided strategy (following US appropriate use criteria).¹⁰ There was no difference in short-term MACE rates or disease detection (positive angiography) rates, between the three strategies.

There is concern that coronary angiography is over-used in the diagnostic pathway of suspected CHD, and that the majority of patients investigated will not have significant obstructive coronary disease.^{6,7} Avoiding unnecessary invasive angiography could have significant financial benefits, avoids exposing patients to unnecessary risk, and is also a strong patient desire.²¹ For this reason we chose this as our patient-focused primary endpoint.

Current international guidelines for investigation and management of suspected CHD all suggest risk stratification for PTL estimation.^{12,22,23} The Duke score, used in NICE guidelines, is based upon the original Diamond Forrester model, but includes additional demographic factors to further stratify risk.¹² These models, derived over three-decades ago, tend to over-estimate CHD risk, as patient demographics, risk factors and treatment have changed considerably over time.²⁴ In CE-MARC 2, the reduction in unnecessary angiography by a CMR (or MPS) strategy appears largely driven by the over-estimation of disease probability from using the Duke score. Current NICE guidelines categorize a pre-test likelihood of 60-90% as being high-risk for CHD, and recommend direct referral for angiography. In CE-MARC 2 this explained the majority of patients in the NICE-

guided group who got referred for angiography (82/102; 80.4%), and the majority of unnecessary angiograms (59/69; 85.5%). This is further emphasized by the pre-planned, combined sub-analysis of functional imaging (CMR or MPS) in the 60-90% (high-risk) PTL population, which showed substantially reduced odds of unnecessary angiography in this group compared to NICE guideline-based care.

Overall, rates of disease detection (positive angiography) were comparable for the three strategies, suggesting no penalty for using functional imaging as a gatekeeper for angiography, even in high-risk subgroups. Consistent with published studies, CE-MARC 2 showed a low overall rate of MACE in a stable chest pain population, with no early difference between strategies.

It remains a point of debate as to whether all of our protocol-defined unnecessary angiograms are truly clinically unnecessary; some would argue that negative tests are the 'price to pay' for not missing important disease in others. This assumes a population perspective, and our trial primary endpoint was derived after close consultation with patient and public representatives: from an individual patient perspective, an angiogram that doesn't change their treatment or their clinical outcome is considered by patients to have been unnecessary. Certainly guidelines are clear that we do not need to undertake angiography to either diagnose angina or offer primary prevention and symptom control.

There have been no randomized trials comparing the performance of current management guidelines and a broad functional imaging approach in terms of important clinical endpoints. Although cross-sectional imaging (CMR and CCT) has improved our diagnostic ability, benefits in terms of health outcomes are harder to demonstrate, partly due to complexity of subsequent treatment effects. Functional versus anatomical assessment as a potential 'gate-keeper' to the catheterization laboratory is a topic of on-going debate.^{25,26} The PROMISE trial showed no improvement in clinical outcomes using CCT versus a variety of functional tests in patients investigated for suspected CHD; whilst the CCT strategy increased rates of cardiac catheterization

(12.2% vs. 8.1%; $P=0.02$) and coronary revascularization.²⁵ This may be important following a recent observational study of 544 US centers showing higher rates of inappropriate percutaneous coronary intervention at sites performing the highest rates of angiography, suggesting anatomical assessment could predispose to unnecessary therapy.²⁷ Although numbers are small, in CE-MARC 2 an increased rate of unnecessary angiography was suggested in the low-risk group in the guidelines-based strategy group, the majority of whom underwent CCT.

Limitations:

The false positive and false negative rates are often quantities of interest in evaluating diagnostic methods. CE-MARC 2 only angiographically verified a subset of patients, contingent on strategy findings, and so cannot provide accurate estimates. The original CE-MARC trial defined the false positive and false negative rates for CMR and MPS, and showed CMR was superior to MPS.¹ In the current study there was no statistical difference between CMR and MPS strategies for reduction in unnecessary angiography, despite the finding from CE-MARC. However, CE-MARC was able to detect small differences due to its paired design (all patients underwent all tests), whereas the current study compared independent groups which confers lower power.

The study population was predominantly white northern European, therefore findings may not translate to other populations; geographic heterogeneity of CHD incidence is well known.²³ At trial initiation, contemporary guidelines used the Duke score,^{3,4} with the NICE guidelines classifying high risk for CHD as 60-90% pre-test likelihood. It is now recognized that this may overestimate CHD risk, such that recent guidelines⁵ have adopted a recalibrated risk model.²³ The primary endpoint was objective (using FFR), although performance was not clinically possible in all cases; blinded core-lab analysis of QCA data avoided subjective visual angiography interpretation. Overall full adherence to the protocol was high, with some unavoidable variation due to individual clinical practice which could introduce bias (e.g. abnormal imaging results not proceeding to angiography). To mitigate this, analysis was by ITT principles and the primary endpoint was

purposely all-inclusive (i.e. false positives, true negatives when not believed by clinicians, and also test failures). The slightly different rates of incomplete data (not statistically significant) between study groups was not of concern, as the data completeness rate was however high overall. Per-protocol and sensitivity analyses (Table S5) did not alter the trial conclusions. Finally, although clinically robust, MACE isn't a proxy for a missed diagnosis/treatment, e.g. missed opportunity for revascularization by not having angiography (due to a false negative result). However, it remains debatable whether revascularization for stable angina has prognostic benefit over optimal medical therapy, which will be answered by the ongoing ISCHEMIA trial.²⁸

Conclusions:

In patients with suspected angina, investigation by CMR produced a lower probability of unnecessary angiography than NICE guideline-directed care, with no statistically significant difference between CMR and MPS strategies. There were no statistically significant differences in MACE rates at 12 months post-randomization.

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CONFLICT OF INTEREST

JPG, DPR, JRF, PB, KM, GPM, SP, EDA, AP, MS, SW, CCE, DAC, LDS and JMB: None declared.

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Table 1. Baseline characteristics of the trial participants by study group.

Characteristic	Total (N=1,202)	NICE-guided Care (N=240)	CMR-guided care (N=481)	MPS-guided care (N=481)
Age, Mean (SD) years	56.3 (9.03)	56.5 (9.21)	56.5 (9.10)	55.9 (8.87)
Female sex, no. (%)	564 (46.9%)	112 (46.7%)	227 (47.2%)	225 (46.8%)
Non-white Ethnicity, no. (%)	95 (7.9%)	19 (7.9%)	38 (7.9%)	38 (7.9%)
Cardiac risk factors				
Body Mass Index, Mean (SD) kg/m ²	29.1 (5.23)	29.0 (5.24)	29.2 (5.36)	29.1 (5.12)
Hypertension, no. (%)	458 (38.1%)	99 (41.3%)	177 (36.8%)	182 (37.8%)
Diabetes, no. (%)	150 (12.5%)	24 (10.0%)	53 (11.0%)	73 (15.2%)
Dyslipidemia, no. (%)	483 (40.2%)	99 (41.3%)	186 (38.7%)	198 (41.2%)
Current or past Smoking, no. (%)	702 (58.4%)	147 (61.3%)	284 (59.0%)	271 (56.3%)
Family history of premature CHD*	651 (54.2%)	140 (58.3%)	252 (52.4%)	259 (53.8%)
Peripheral Vascular Disease, no. (%)	27 (2.2%)	10 (4.2%)	8 (1.7%)	9 (1.9%)
Cerebrovascular disease, no. (%)	42 (3.5%)	8 (3.3%)	17 (3.5%)	17 (3.5%)
Nature of Angina, no. (%)				
Atypical	801 (66.6%)	158 (65.8%)	318 (66.1%)	325 (67.6%)
Typical	401 (33.4%)	82 (34.2%)	163 (33.9%)	156 (32.4%)
Risk Burden				
PTL, Mean (SD) %†	49.5% (23.78%)	50.7% (23.28%)	49.9% (24.25%)	48.6% (23.57%)
PTL 10-29%††	314 (26.1%)	61 (25.4%)	128 (26.6%)	125 (26.0%)
PTL 30-60%††	450 (37.4%)	88 (36.7%)	179 (37.2%)	183 (38.0%)
PTL 61-90%††	438 (36.4%)	91 (37.9%)	174 (36.2%)	173 (36.0%)
No. risk factors/patient, Mean (SD)	2.0 (1.13)	2.1 (1.05)	2.0 (1.18)	2.0 (1.11)
10yr ASCVD risk >7.5%‡	441/923 (47.8%)	93/179 (52.0%)	175/377 (46.4%)	173/367 (47.1%)
Medications, no. (%)				
Antiplatelet therapy	689 (57.3%)	150 (62.5%)	271 (56.3%)	268 (55.7%)
Beta Blocker	381 (31.7%)	74 (30.8%)	150 (31.2%)	157 (32.6%)
Statin or other lipid lowering therapy	500 (41.6%)	108 (45.0%)	191 (39.7%)	201 (41.8%)
Angiotensin Converting Enzyme inhibitor or Angiotensin II Receptor Blocker	303 (25.2%)	66 (27.5%)	115 (23.9%)	122 (25.4%)
Other anti-anginal medication	701 (58.3%)	142 (59.2%)	283 (58.8%)	276 (57.4%)

* Family history of premature CHD defined as diagnosis of the disease in a male first-degree relative before 55 years of age or in a female first-degree relative before 65 years of age.

† According to Pryor et al.¹²

†† Categories used to decide stratification in the NICE Guidelines group.

‡ According to edibility criteria of Goff et al.²⁰

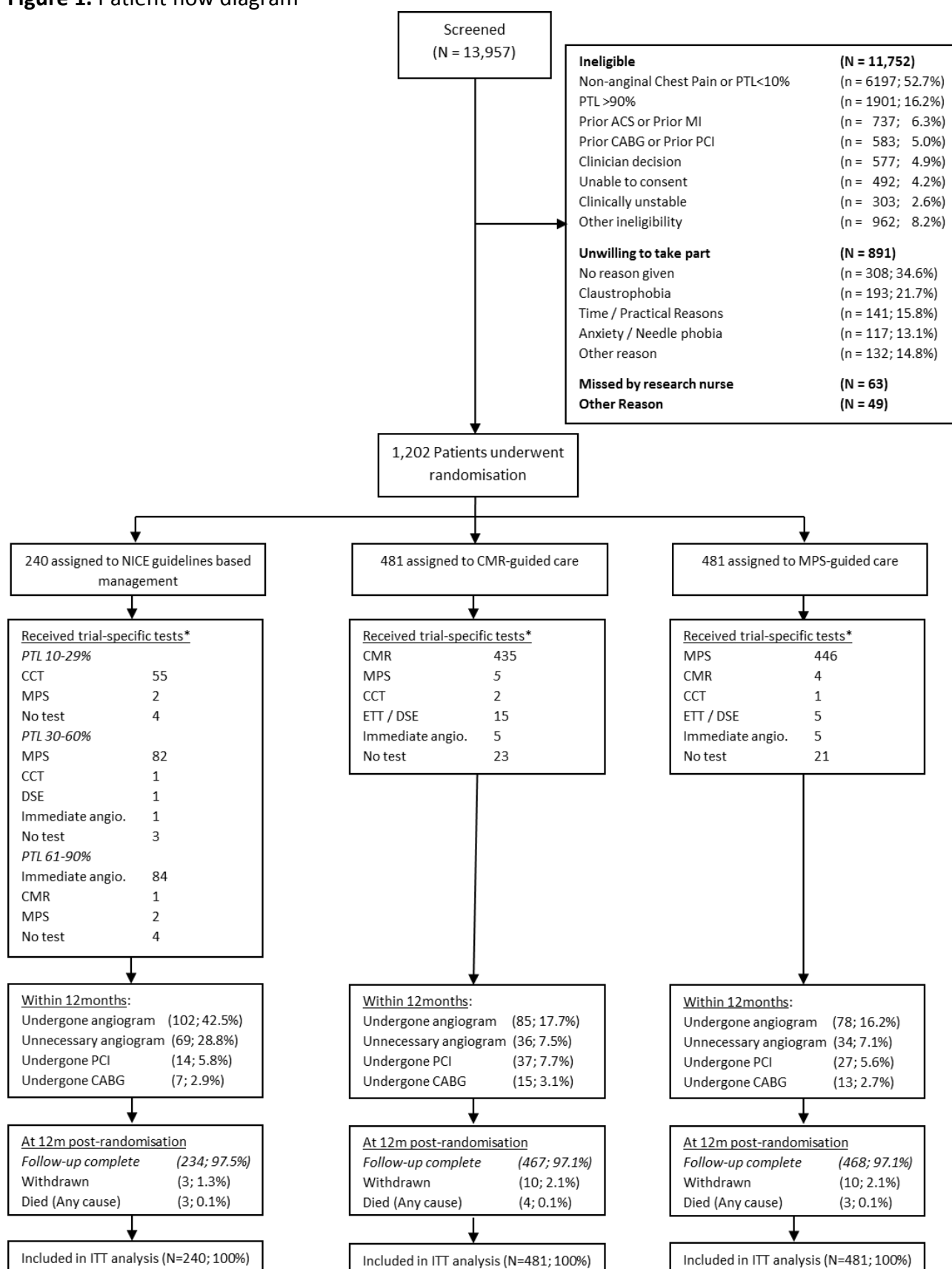
ASCVD, atherosclerotic cardiovascular disease; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker.

Table 2. Summary of trial endpoints.

					Absolute Differences (95% Confidence Interval)	
	Total (N=1,202)	NICE-guided care (N=240)	CMR-guided care (N=481)	MPS-guided care (N=481)	CMR vs NICE	CMR vs MPS
Primary endpoint						
Unnecessary invasive angiography	139 (11.6%)	69 (28.8%)	36 (7.5%)	34 (7.1%)	-21.3% (-28.7%, -13.6%)	0.4% (-6.0%, 6.8%)
Components of the primary endpoint						
False positive non-invasive test	35	5	18	12	-	-
Direct to angiography (by strategy)	59	59	-	-	-	-
Negative test, non per-protocol	41	5	15	21	-	-
Inconclusive test/result	4	-	3	1	-	-
Secondary endpoints						
Positive angiography occurrence	118 (9.8%)	29 (12.1%)	47 (9.8%)	42 (8.7%)	-2.3% (-10.0%, 5.4%)	1.0% (-5.4%, 7.5%)
False positive non-invasive test	73	4	38	31	-	-
Direct to angiography (by strategy)	23	23	-	-	-	-
Negative non-invasive test, non per-protocol	9	1	2	6	-	-
Inconclusive non-invasive test/result	2	-	2	-	-	-
Acute/urgent Angio indication	9	1	4	4	-	-
Angio as alternative initial investigation	2	-	1	1	-	-
Major Adverse Cardiovascular Events						
Events (Patients)	44 (36)	7 (6)	20 (15)	17 (15)	1.0% (-6.7%, 8.8%)	0.0% (-6.4%, 6.4%)
Cardiovascular death	5	1*	1	3	-	-
Myocardial Infarction	9	2	5	2	-	-
Revascularization - Unplanned PCI	12	2	6	4	-	-
Revascularization - Unplanned CABG	1	-	1	-	-	-
Arrhythmia	9	2	4	3	-	-
Heart Failure	4	-	-	4	-	-
Stroke/TIA	4	-	3	1	-	-

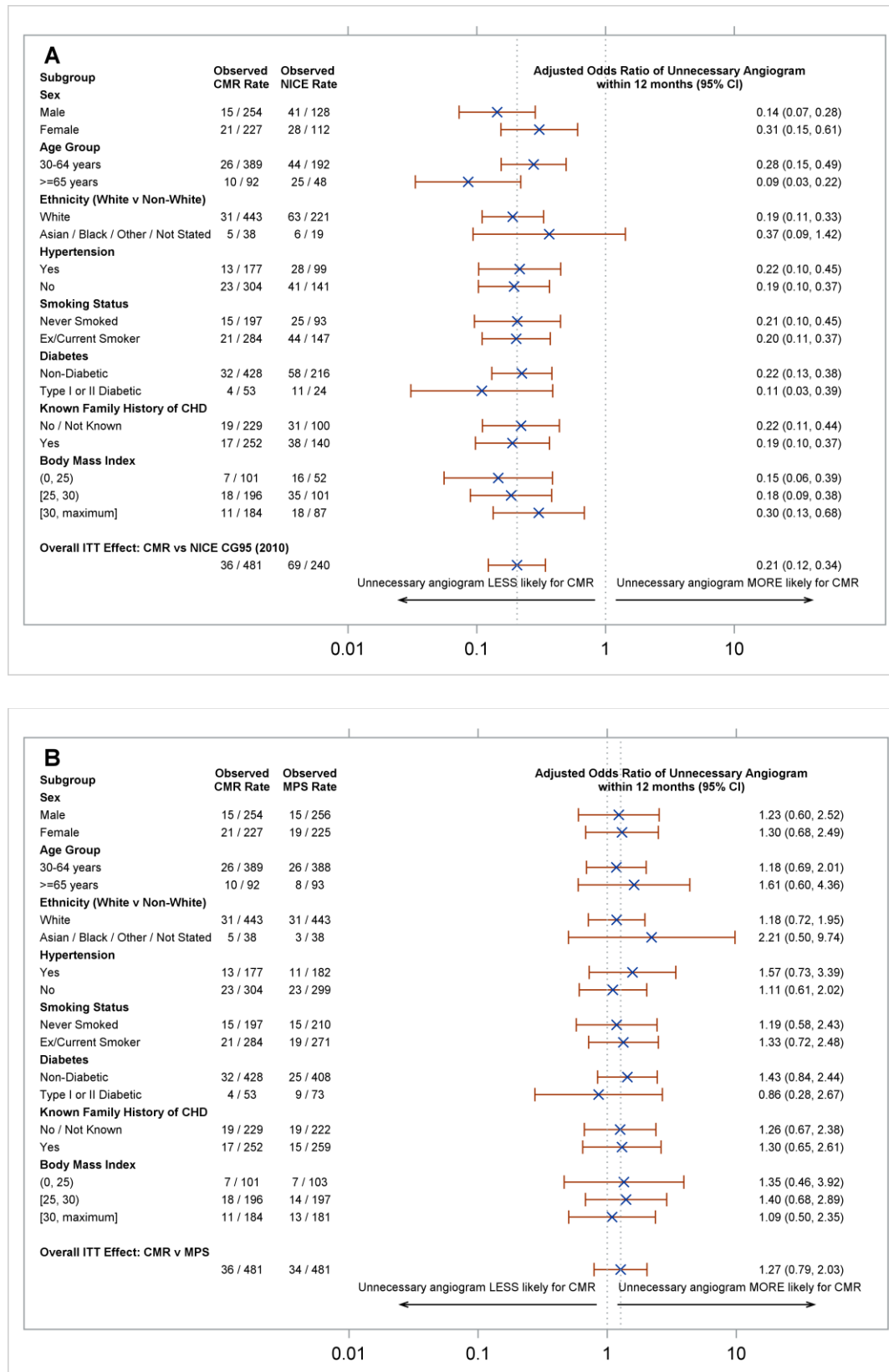
* This event occurred 2 days after the 3-year cut-off, so is excluded from summaries of absolute MACE rates at 3 years. All other events occurred within 3 years of randomization. # 3-year MACE rates include all participants (median follow-up 16 months). PCI, Percutaneous Coronary Intervention; CABG, Coronary Artery Bypass Graft; TIA Transient Ischemic Attack

Figure 1. Patient flow diagram



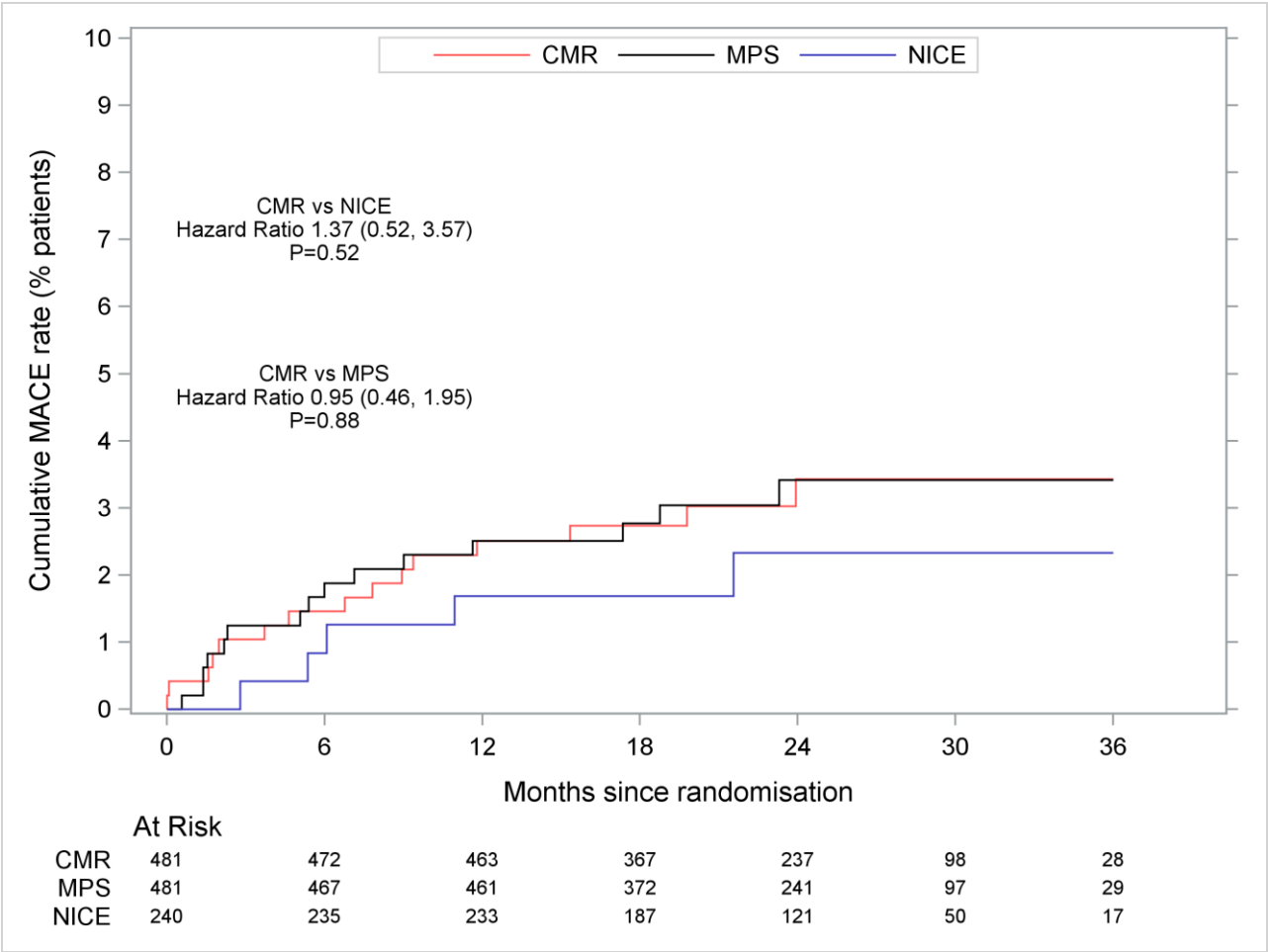
ACS, acute coronary syndrome; MI, myocardial infarction; CMR, cardiovascular magnetic resonance; MPS myocardial perfusion scintigraphy; CCT, cardiac computed tomography; ETT, exercise treadmill test; DSE, dobutamine stress echo; PCI, percutaneous coronary intervention, CABG, coronary artery bypass grafting; ITT, intention to treat; *patients may have received more than one test, in addition to or as an alternative to their strategy.

Figure 2. Forest plots for the effect of gender, age, ethnicity, hypertension, smoking, diabetes, family history and body mass index, for A) CMR vs. NICE, B) CMR vs. MPS.



Unnecessary angiography figures quoted are the frequencies observed within each subgroup.

Figure 3. Kaplan-Meier event curves for time to first MACE after a minimum of 12 month follow up from randomization (median 16 months).



Hazard ratios for time to first MACE (and Likelihood Ratio test P-Values) calculated by Cox Proportional hazards modelling, adjusted for randomizing center, age category, sex, pre-test likelihood category, hypertension, ethnicity, diabetes, and smoking status.